Translation

PCT/EP2003/013008

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 039PCT 1683 | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/EP2003/013008 | International filing date (*day/month/year*) 20 November 2003 (20.11.2003) | Priority date (*day/month/year*) 24 March 2003 (24.03.2003) |
| International Patent Classification (IPC) or national classification and IPC A61K 31/7072 | | |
| Applicant RESPROTECT GMBH | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 28 April 2004 (28.04.2004) | 29 June 2005 (29.06.2005) |
| Name and mailing address of the IPEA/EP<br><br>Facsimile No. | Authorized officer<br><br>Telephone No. |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/013008

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-13, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-7, filed with the letter of 13 October 2004 (13.10.2004)

☒ the drawings:

pages 1/6-6/6, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

An international preliminary examination report is not established for aspects of the invention in respect of which no search report has been carried out.

1. The current claims 1-5 and 7 relate to an inordinately large number of possible compounds, of which only a small proportion are supported by the description (PCT Article 6) or can be regarded as having been disclosed in the application (PCT Article 5): protective forms and prodrugs of BVDU.

In the present case the claims lack the proper support and the application lacks the requisite disclosure.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-7 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | 1-7 | YES |
| | Claims | | NO |
| Industrial applicability (IA) | Claims | 1-7 | YES |
| | Claims | | NO |

2. Citations and explanations

1. This international preliminary examination report makes reference to the following search report citations (D) (please refer to the search report for the cited passages):

D1: WO 01/07088 A (SHEPARD H MICHAEL; NEWBIOTICS INC (US)) 1 February 2001 (2001-02-01)

D2: WO 96/23506 A (FAHRIG RUDOLF; FRAUNHOFER GES FORSCHUNG (DE); STEINKAMP ZUCHT ANGE) 8 August 1996 (1996-08-08)

D3: CLERCQ DE E: "POTENTIAL OF BROMOVINYLDEOXYURIDINE IN ANTICANCER CHEMOTHERAPY" ANTICANCER RESEARCH, HELENIC ANTICANCER INSTITUTE, ATHENS, GR, Vol. 6, No. 4, July 1986 (1986-07), pages 549-557, XP001070144 ISSN: 0250-7005

D4: FAHRIG, RUDOLF ET AL: "Prevention of adriamycin-induced mdr1 gene amplification and expression in mouse leukemia cells by simultaneous treatment with the anti-recombinogen bromovinyldeoxyuridine" ANTI-CANCER DRUG DESIGN (2001), VOLUME DATE 2000 , 15(5), 307-312, XP008030116

D5: BALZARINI J ET AL: "INCREASED SENSITIVITY OF THYMIDINE KINASE-DEFICIENT (TK-) TUMOR CELL LINES TO THE CELL GROWTH INHIBITORY EFFECTS OF (E)-5-(2-

BROMOVINYL)-2'-DEOXYURIDINE (BVDU) AND RELATED COMPOUNDS" ANTICANCER RESEARCH, HELENIC ANTICANCER INSTITUTE, ATHENS, GR, Vol. 6, No. 5, 1986, pages 1077-1084, XP008030090 ISSN: 0250-7005

D6: IIGO M ET AL: "EFFECT OF (E)-5-(2-BROMOVINYL)-2'-DEOXYURIDINE ON LIFE-SPAN AND 5-FLUOROURACIL METABOLISM IN MICE WITH HEPATIC METASTASES" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, Vol. 26, No. 10, 1990, pages 1089-1092, XP008030091 ISSN: 0959-8049

D7: DEGREVE, B. ET AL: "Selection of HSV-1 TK gene-transfected murine mammary carcinoma cells resistant to (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU and ganciclovir (GCV)" GENE THERAPY (2000), 7(18), 1543-1552, XP001190852.

2. The applicant's attention is drawn to the fact that the present opinion of the Examining Authority refers only to aspects which are a subject of the international search report (aspects concerning the compound BVDU and the prodrug in claim 6).

3. The amendments submitted on 8 October 2004 meet the requirements of PCT Article 19(2) and 34(2)(b): the basis for the new claim 1 are the original claims 10 and 1 and the disclosures on page 4, paragraph 5, and page 5, lines 26-28.

**Novelty**

Claims 1-7 are novel under PCT Article 33(2).

4.1 Document D1 describes the use of BVDU and a BVDU prodrug together with fluoropyrimidines or Tomudex in the treatment of neoplastic cells (see document D1, pages 15-

16 (wherein a preferred administration of BVDU with 5-FU is disclosed): "this invention provides the methods described, wherein an effective amount of another agent is coadministered with the substrate drug (BVDU) of this invention"; see also table 4, page 73, wherein NB1011, the prodrug of BVDU, has a high IC50 value, which indicates the absence of an antineoplastic activity.

However, document D1 also describes the activity of BVDU alone, without additional substances, against cancer and cancer cells resistant to 5-FU (see D1, page 8, and page 12, paragraph 2). However, an activity of this kind appears always to be connected to the administration of a further antineoplastic compound. Claims 1-7 are therefore novel with respect to document D1 (PCT Article 33(2)).

4.2 Documents D2 to D4 likewise describe the activity of BVDU together with other antineoplastic compounds. The applicant has demonstrated that when BVDU is administered alone after completion of a chemotherapy, cell growth is inhibited more than if the chemotherapy had been continued with cytostatic agents.

Claims 1-7 are therefore novel over documents D2 to D4 (PCT Article 33(2)).

4.3 Document D5 describes the activity of BVDU and prodrugs alone used *in vitro* against the growth of breast cancer cells and leukaemia cells. If the use of a compound for the treatment of a disease in a particular group of individuals is known (in the present case patients having already undergone chemotherapy), the treatment of the same disease using the same compound constitutes a new therapeutic use if it is administered to a different group of individuals which physiologically or pathologically

differs from the first group.

In the present case, document D5 discloses only an *in vitro* activity, whereas the present application describes the activity of BVDU after the completion of anti-cancer chemotherapy (inhibition of chemoresistance and increase in chemosensitivity) (see page 5, lines 31-35). Consequently, claims 1-7 are novel over document D5 (PCT Article 33(2)).

**Inventive step**

5. Claims 1-7 are inventive within the meaning of PCT Article 33(3)

A person skilled in the art would have no reason to administer a substance, in this case BVDU, after a chemotherapy since document D1 offers nothing to suggest that BVDU itself could have an activity, that BVDU has this activity after a chemotherapy, and that the effect is the same if the chemotherapy is continued. According to document D1, BVDU does not appear to have any anti-cancer activity.